The Benefit of Treating Isolated Systolic Hypertension

Ji-Guang Wang, MD, and Jan A. Staessen, MD, PhD

Address
Study Coordinating Center, Hypertension and Cardiovascular Rehabilitation Unit, Department of Molecular and Cardiovascular Research, University of Leuven, B-3000 Leuven, Belgium.
E-mail: jan.staessen@med.kuleuven.ac.be

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Isolated systolic hypertension affects over 15% of all people older than 60 years of age. In the elderly, systolic hypertension is a major modifiable cardiovascular risk factor. Systolic blood pressure is associated with higher risk of an adverse outcome. Diastolic blood pressure is inversely correlated with total mortality, independent of systolic blood pressure, highlighting the role of pulse pressure as risk factor. Three placebo-controlled outcome trials on antihypertensive drug treatment in older patients with isolated systolic hypertension have been published: the Systolic Hypertension in the Elderly Program (SHEP), the Systolic Hypertension in Europe (Syst-Eur) Trial, and the Systolic Hypertension in China (Syst-China) Trial. These three trials showed the benefit of antihypertensive drug treatment. A meta-analysis was done by pooling the patients from these three trials with a subset of patients with isolated systolic hypertension from five other trials in the elderly. The pooled results of 15,693 older patients with isolated systolic hypertension prove that antihypertensive drug treatment is justified if systolic blood pressure on repeated clinic measurements is 160 mm Hg or higher.

Introduction

Systolic blood pressure increases with age until the eighth or ninth decade of life [1–3]. In contrast, diastolic blood pressure increases only until middle age; in the elderly, it either levels off or may even decrease slightly. The divergent trends in systolic and diastolic blood pressure have been observed in cross-sectional [1,2] and longitudinal [1,3] studies, and explain why pulse pressure and the prevalence of isolated systolic hypertension increase curvilinearly with age. In western countries, the prevalence of isolated systolic hypertension averages 8% in sexagenarians and exceeds 25% in elderly people older than 80 years of age [1]. Isolated systolic hypertension is a distinct pathologic entity in which the increase in systolic blood pressure is mainly due to decreased elasticity of the large arteries and is not necessarily accompanied by an increase in mean arterial blood pressure or in peripheral resistance [1].

Blood Pressure As a Risk Factor

Among the cardiovascular risk factors amenable to prevention in the elderly, systolic hypertension is of great importance [1]. In a recent comprehensive overview of trials in isolated systolic hypertension [4••], the risk conferred by systolic and diastolic blood pressure at baseline was evaluated both before and after correction for regression dilution bias [5,6]. Untreated patients (n = 7757) with isolated systolic hypertension from eight trials on antihypertensive drug treatment in the elderly [7–14] were pooled. In a multiple Cox regression analysis stratified for trial and adjustment for sex, age, smoking, and previous cardiovascular complications, total mortality was positively correlated with systolic blood pressure at baseline (P = 0.0001), whereas the association with diastolic blood pressure was negative (Table 1).

With use of the same stratified and adjusted Cox model as for total mortality, the relative hazard rates associated with a 10-mm Hg increase in the baseline systolic blood pressure were 1.12 (P = 0.02) for stroke but only 1.04 (P = 0.37) for coronary events. Diastolic blood pressure at baseline tended to be inversely correlated with cardiovascular mortality; the relative hazard rate associated with a 5-mm Hg increase was 0.95 (P = 0.08). However, diastolic blood pressure was not significantly associated with outcome if fatal and nonfatal events were combined (Table 1). These findings highlight the importance of pulse pressure as a risk factor. Indeed, both this [4••] and other studies [15,16] showed that at any given systolic blood pressure, a lower diastolic blood pressure was associated with a higher risk of events [4••].

After correction for regression dilution bias [5,6], the relative hazard rates associated with a 10-mm Hg increase in systolic blood pressure were 1.26 (P = 0.0001) for total mortality and 1.22 (P = 0.02) for stroke, but only 1.07 (P = 0.37) for coronary events. These findings were confirmed by the nonparametric approach, which compared the risk of an adverse outcome in each quintile of blood pressure with the overall risk in all patients using the deviation-from-means coding method (Fig. 1) [4••].

Table 1. Relative hazard rates in 7757 control patients associated with baseline and usual blood pressures

Event	Events, *n*	Relative hazard rates associated with blood pressure (95% CI)*		
		Baseline blood pressure	Usual blood pressure†	*P* value
Increase in systolic pressure > 10 mm Hg				
All-cause mortality	734	1.14 (1.07–1.21)	1.26 (1.13–1.40)	0.0001
Cardiovascular deaths	392	1.12 (1.03–1.21)	1.22 (1.06–1.40)	0.007
Cardiovascular events	835	1.08 (1.02–1.15)	1.15 (1.04–1.28)	0.01
Stroke	387	1.12 (1.02–1.21)	1.22 (1.04–1.40)	0.02
Coronary events	373	1.04 (0.95–1.14)	1.07 (0.91–1.26)	0.37
Increase in diastolic pressure > 5 mm Hg				
All-cause mortality	734	0.96 (0.92–1.00)	0.95 (0.89–1.00)	0.05
Cardiovascular deaths	392	0.95 (0.89–1.01)	0.93 (0.86–1.01)	0.08
Cardiovascular events	835	0.99 (0.95–1.03)	0.98 (0.93–1.04)	0.54
Stroke	387	0.99 (0.93–1.05)	0.98 (0.90–1.06)	0.66
Coronary events	373	1.00 (0.94–1.07)	1.00 (0.91–1.09)	0.99

* The Cox regression models were stratified for trial. The relationships between outcome and systolic or diastolic blood pressure were adjusted for each other and for sex and age.
† The usual blood pressure was measured in 5489 control patients with event-free survival of 2 years. Correction for regression dilution bias increased the slopes of the outcomes on systolic and diastolic blood pressures by 90% and 40%, respectively.
Adapted from Staessen *et al.* [4 ••]; with permission.

Trials in Isolated Systolic Hypertension

The goal of treating elderly patients with hypertension is not to reduce their blood pressure but to prevent the cardiovascular complications of hypertension so that longevity increases and quality of life improves. The 1990s witnessed the publication of three outcome trials [7–9] that specifically studied whether cardiovascular risk in elderly patients is reversible by antihypertensive drug treatment.

Systolic Hypertension in the Elderly Program

The principal results of the Systolic Hypertension in the Elderly (SHEP) trial were published in 1991 [7]. The study participants were 4736 patients (1.1%) from among 447,921 individuals (aged 60 years or more) who were screened; the participants were randomly assigned to treatment with the thiazide diuretic chlorthalidone (12.5–25 mg/d) (n = 2365), with the possible addition of atenolol (25–50 mg/d) and reserpine (0.05–0.1 mg/d) or to matching placebo (n = 2371). Systolic blood pressure ranged from 160 to 219 mm Hg, and diastolic blood pressure was less than 90 mm Hg. Mean blood pressure at baseline was 170 mm Hg systolic and 77 mm Hg diastolic.

The mean duration of follow-up was 4.5 years. The 5-year systolic blood pressure averaged 155/72 mm Hg in the placebo group and 143/68 mm Hg in the active treatment group. Active treatment reduced total stroke incidence from 16.4 to 10.4 events per 1000 patient-years by 36% (95% CI, 18%–50%; $P < 0.001$). Drug treatment also decreased nonfatal stroke by 37% (95% CI, 18%–51%), nonfatal myocardial infarction by 33% (95% CI, 4%–53%), nonfatal myocardial infarction combined with coronary death by 27% (95% CI, 6%–43%), and all cardiovascular complications by 32% (95% CI, 21%–42%). Total mortality was not significantly influenced (change, -13% [95% CI, -27%–5%). The 5-year absolute benefit with regard to stroke and major cardiovascular complications amounted to 30 and 55 events per 1000 participants, respectively, and was equally observed in all stratification groups.

In the SHEP trial, active treatment decreased the incidence of all cardiovascular complications to the same extent (change, -34%) in 583 diabetic patients (95% CI, -54% to -6%) and 4149 nondiabetic patients (95% CI, -45% to -21%) [17]. The overall incidence of dementia was similar in the two treatment groups: In 37 patients (1.6%) receiving active treatment and 44 (1.9%) receiving placebo, dementia was diagnosed and confirmed by the specialized coding panel [7].

Systolic Hypertension in Europe Trial

As in the SHEP trial [7], patients eligible for enrollment in the Systolic Hypertension in Europe (Syst-Eur) trial [8] were at least 60 years of age. At three run-in visits 1 month apart, the patients' sitting systolic blood pressure while they were taking single-blinded placebo averaged from 160 to 219 mm Hg, with diastolic blood pressure lower than 95 mm Hg. After stratification for study center, sex, and previous cardiovascular complications, 4695 patients were randomly assigned to active treatment or placebo. Active treatment consisted of nitrendipine (10–40 mg/d), with the possible addition of enalapril (5–20 mg/d) and hydrochlorothiazide (12.5–25 mg/d), titrated or combined to reduce the sitting systolic blood pressure by at

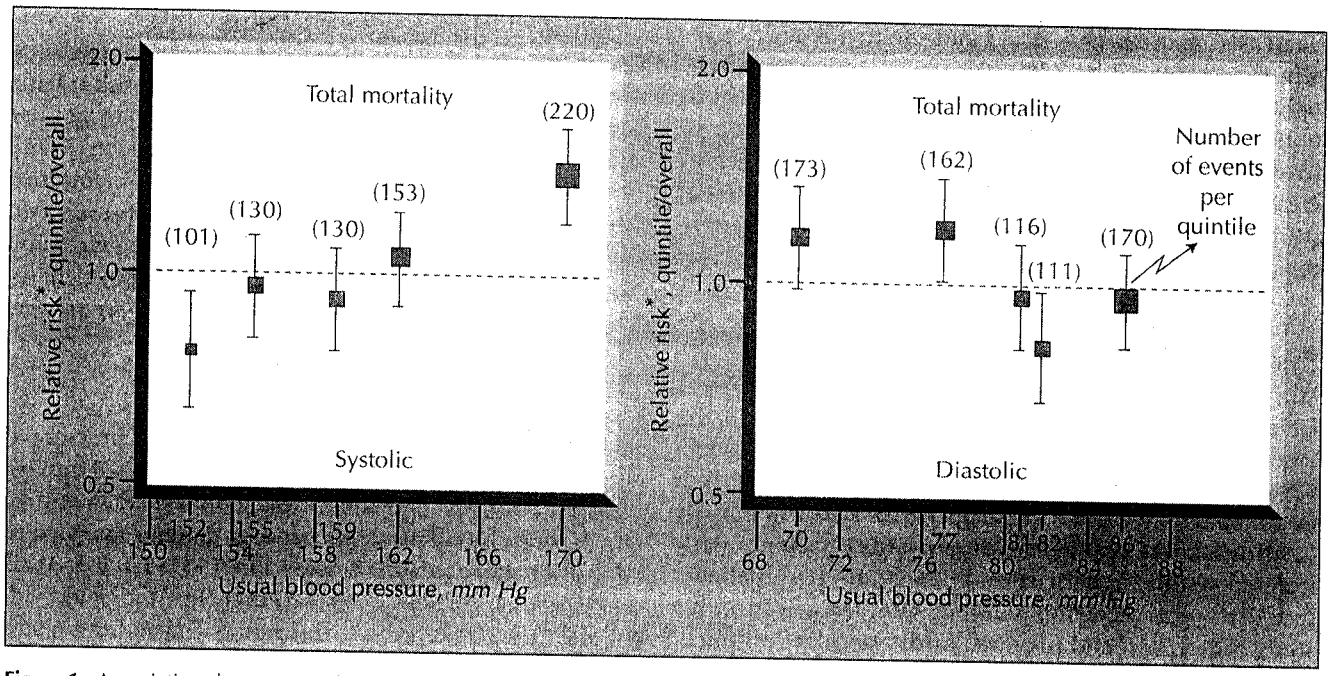

Figure 1. Associations between total mortality and usual blood pressure in 7757 control patients. Solid squares represent risks in quintiles of blood pressure distribution relative to overall risk in all patients. The size of the squares is proportional to the number of events in each quintile. Vertical lines denote 95% CIs. *Adjusted for sex, age, and trial. (*Adapted from* Staessen *et al.* [4••]; with permission.)

least 20 mm Hg to below 150 mm Hg. Matching placebo tablets were used similarly.

At 2 years (median follow-up), the sitting systolic blood pressure decreased by 13/2 mm Hg in the placebo group (n = 2297) and by 23/7 mm Hg in the active treatment group (n = 2398). The between-group differences in blood pressure amounted to 10.1/4.5 mm Hg ($P < 0.001$). Active treatment reduced the incidence of fatal and nonfatal stroke (primary endpoint) from 13.7 to 7.9 events per 1000 patient-years by 42% (95% CI, 17%–60%; $P = 0.003$). During active treatment, the rate of all cardiac endpoints decreased by 26% (95% CI, 3%–44%; $P = 0.03$) and the rate of all cardiovascular endpoints by 31% (95% CI, 14%–45%; $P < 0.001$). Cardiovascular mortality was slightly lower with active treatment (-27%; $P = 0.07$), but all-cause mortality was not influenced (-14%; $P = 0.22$). Treating 1000 patients for 5 years could prevent 29 strokes or 53 major cardiovascular events.

In subgroup analyses [18], the benefit of antihypertensive treatment for total ($P = 0.009$) and cardiovascular ($P = 0.09$) mortality weakened with advancing age and the benefit for total mortality decreased with lower systolic blood pressure at study entry ($P = 0.05$). The benefits of active treatment were not independently related to sex or to the presence of cardiovascular complications at entry. Antihypertensive treatment was more effective in 492 diabetic patients than in 4203 patients without diabetes at entry [19]. After adjustment for possible confounders, in the diabetic patients, total mortality was reduced by 55% (95% CI, 15%–76%), cardiovascular mortality by 76% (95% CI, 33%–91%), all cardiovascular endpoints by 69% (95% CI, 41%–84%), fatal and nonfatal stroke by 73% (95% CI, 26%–90%), and all cardiac endpoints by 63% (95% CI, 10%–85%). In nondiabetic patients, active treatment decreased all cardiovascular endpoints by 26% (95% CI, 6%–41%) and fatal and nonfatal stroke by 38% (95% CI, 8%–58%). Active treatment reduced total mortality, cardiovascular mortality, and all cardiovascular endpoints significantly more in diabetic than in the nondiabetic patients (P = 0.04, 0.02, and 0.01, respectively) [19].

Further analyses also suggested benefit in patients who were taking nitrendipine as the sole therapy [20]. The per-protocol analysis largely confirmed the intention-to-treat results [19]. Active treatment reduced all strokes by 44% ($P = 0.004$), all cardiac endpoints by 26% ($P = 0.05$) and all cardiovascular endpoints by 32% ($P < 0.001$). Total mortality was reduced by 26% ($P = 0.05$), but a similar reduction in cardiovascular mortality did not reach statistical significance in this analysis.

In the Vascular Dementia Project [21,22,23•,24] of the Syst-Eur trial, 32 incident cases of dementia were observed: 23 cases of Alzheimer's disease, seven of mixed dementia, and two of vascular dementia. Compared with placebo (n = 1180), active treatment (n = 1238) reduced the incidence of dementia by 50% (95% CI, 0%–76%; $P = 0.05$) from 7.7 to 3.8 cases per 1000 patient-years.

In a post hoc analysis of the Syst-Eur trial, changes in renal function were compared in 2258 treated and 2148 untreated patients, of whom 455 had diabetes mellitus and 390 had proteinuria at baseline [25]. During follow-up (median, 2 years), the incidence of mild renal dysfunction (serum creatinine level at least 176.8 μmol/L) in the patients randomly assigned to receive active treatment

decreased by 64% ($P = 0.04$) and the incidence of proteinuria decreased by 33% ($P = 0.03$). Active treatment reduced the risk of proteinuria more in diabetic than in nondiabetic patients (71% vs 20%; $P = 0.04$). In nonproteinuric patients, active treatment did not influence serum creatinine levels, whereas in patients with proteinuria at study entry, serum creatinine levels decreased with active treatment ($P < 0.001$).

Systolic Hypertension in China Trial

Isolated systolic hypertension occurs in around 8% of Chinese people 60 years of age or older [26]. In 1988, the Systolic Hypertension in China (Syst-China) Collaborative Group started to investigate whether antihypertensive drug treatment could reduce the incidence of stroke and other cardiovascular complications in older patients with isolated systolic hypertension [9,26,27,28•]. All patients initially began receiving placebo. After stratification for study center, sex, and previous cardiovascular complications, alternate patients ($n = 1253$) were assigned to receive nitrendipine (10–40 mg/d), with the possible addition of captopril (12.5–50 mg/d) or hydrochlorothiazide (12.5–50 mg/d) or both. These study medications were titrated or combined to reduce the sitting systolic blood pressure by at least 20 mm Hg to below 150 mm Hg. In the remaining 1141 control patients, matching placebos were administered similarly.

At study entry, sitting blood pressure averaged 170 mm Hg systolic and 86 mm Hg diastolic. The mean age was 66.5 years, and the mean total serum cholesterol level was 5.1 mmol/L [9]. At 2 years of follow-up, the sitting systolic and diastolic blood pressure had decreased by 11 mm Hg and 2 mm Hg in the placebo group and by 20 mm Hg and 5 mm Hg in the active treatment group. The between-group differences in systolic and diastolic blood pressure were 9.1/3.2 mm Hg. Active treatment reduced total stroke by 38%—from 20.8 to 13.0 endpoints per 1000 patient-years—(95% CI, 9%–58%; $P = 0.01$), all-cause mortality by 39% (95% CI, 16%–57%; $P = 0.003$), cardiovascular mortality by 39% (95% CI, 4%–61%; $P = 0.03$), stroke mortality by 58% (95% CI, 14%–80%; $P = 0.02$), and all fatal and nonfatal cardiovascular endpoints by 37% (95% CI, 14%–53%; $P = 0.004$). Treatment of 1000 Chinese patients for 5 years could prevent 55 deaths, 39 strokes, or 59 major cardiovascular endpoints [9,29].

A subsequent subgroup analysis showed that the benefit of antihypertensive treatment was particularly evident in diabetic patients, and that for cardiac endpoints the benefit tended to be slightly larger in nonsmokers [28•]. Otherwise, the benefit of active treatment was not significantly influenced by the characteristics of the patients at entry into the Syst-China trial [28•,30].

Quantitative Overview of Trials

The relative and absolute benefit of antihypertensive drug treatment with and without stratification for the risk at baseline was further evaluated in a meta-analysis [4••] by pooling individual patients with isolated systolic hypertension [7–14]. The analysis included all patients of the above-mentioned three outcome trials in isolated systolic hypertension [7–9] and a subset of patients with isolated systolic hypertension enrolled in five other trials [10–14] in the elderly. In eight trials, 15,693 patients with isolated systolic hypertension were followed up for a median of 3.8 years.

Overall effects of antihypertensive treatment

In all 15,693 patients, the mean (±SD) blood pressure at enrollment was 174 ± 12 mm Hg systolic and 83 ± 9 mm Hg diastolic. The mean baseline-corrected differences in systolic and diastolic blood pressures between patients assigned to control or active treatment were 10.4 (95% CI, 9.8–11.0) mm Hg and 4.1 (95% CI, 3.8–4.4) mm Hg. Among individual trials, the blood pressure differences ranged from 6.9 to 18.2 mm Hg systolic and from 2.3 to 8.3 mm Hg diastolic. Overall, the net reductions in systolic and diastolic blood pressures expressed as a percentage of the values at baseline averaged 5.96% (95% CI, 5.63%–6.28%) and 4.91% (95% CI, 4.44%–5.38%), respectively.

Among 7757 control patients, 734 died and 835 had major cardiovascular complications; in 7936 patients allocated to active treatment, these numbers were 656 and 647, respectively. Across all trials, active treatment reduced total mortality (Fig. 2) by 13% (95% CI, 2%–22%; $P = 0.02$) and cardiovascular deaths by 18% (95% CI, 4%–29%; $P = 0.01$). The pooled reduction in fatal combined with nonfatal events was 26% (95% CI, 17%–34%; $P < 0.0001$) for all cardiovascular complications, 30% (95% CI, 18%–41%; $P < 0.0001$) for stroke, and 23% (95% CI, 10%–34%; $P = 0.001$) for coronary events (Fig. 3).

Effects in lower- and higher-risk patients

The patients were subdivided into lower-risk and higher-risk groups based on sex and the following baseline characteristics: age, systolic blood pressure, pulse pressure, the presence of previous cardiovascular complications, and current smoking. Relative benefit was similar across these strata for all events.

In terms of absolute benefit, active treatment was particularly effective in men, older patients, and patients with previous cardiovascular complications. To prevent one major fatal or nonfatal cardiovascular event, the number of patients to treat for 5 years was 18 in men versus 38 in women, 19 in patients 70 years of age or older versus 39 in those 60 to 69 years of age, and 16 in patients with previous cardiovascular complications versus 37 in those without such complications. The number of patients to treat to prevent one cardiovascular death was 63 if pulse pressure at baseline was 90

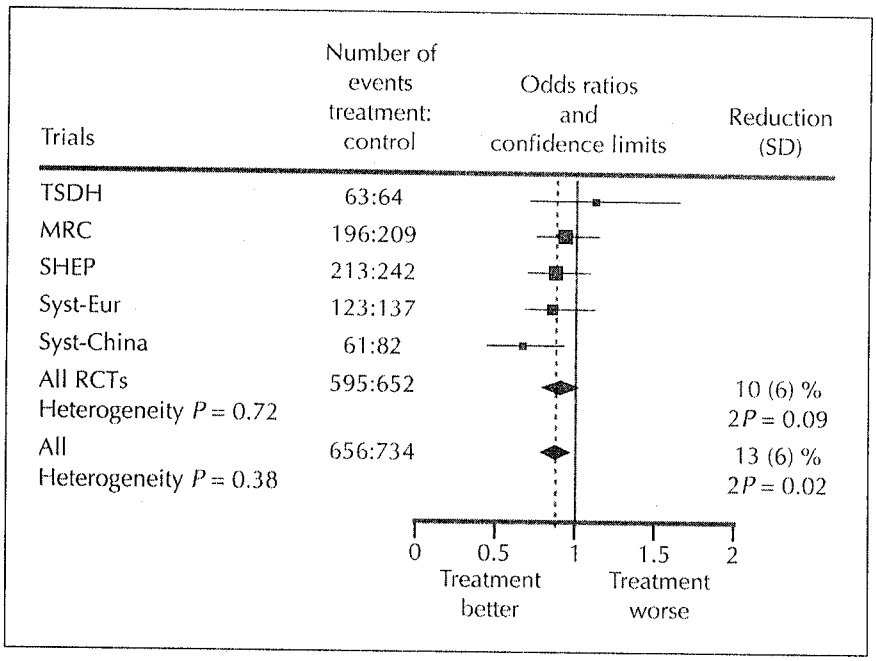

Figure 2. Effects of treatment on total mortality. Solid squares represent treatment-to-control odds ratios in trials; the size of the squares is proportional to the number of events. RCTs—randomized controlled trials. (*Adapted from* Staessen *et al.* [4••]; with permission.)

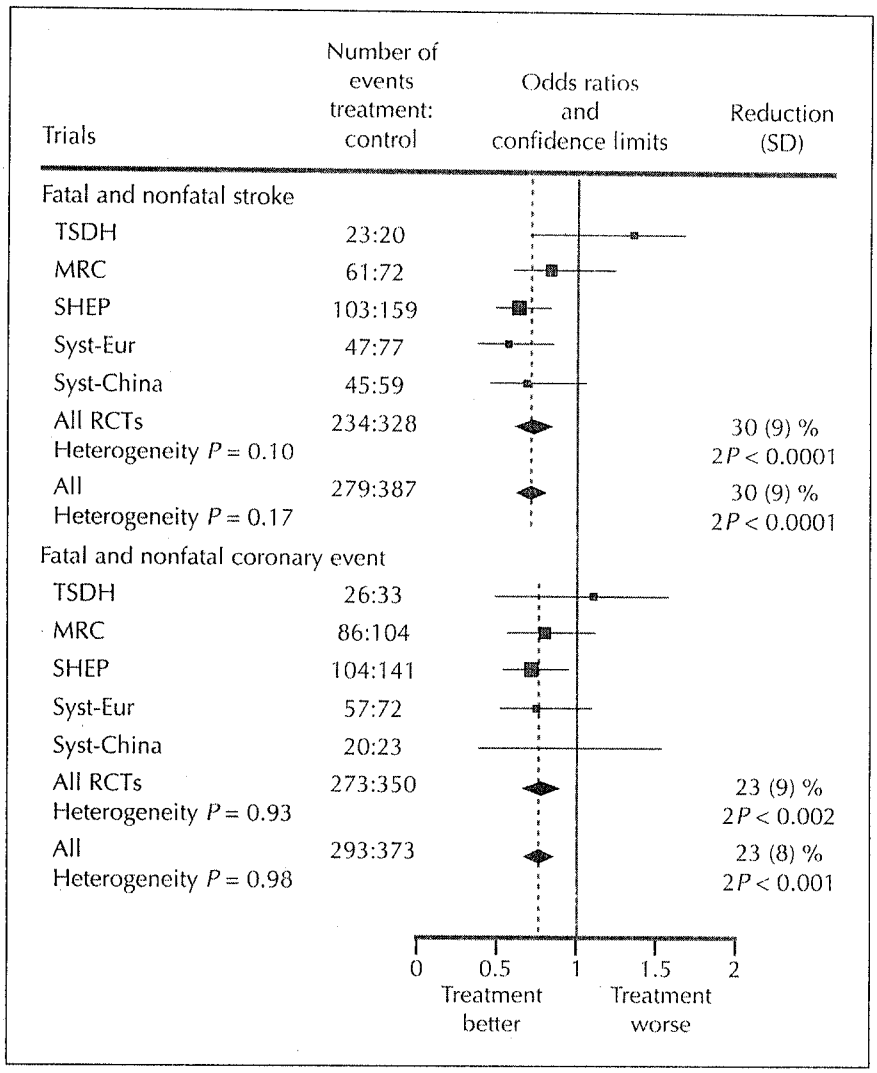

Figure 3. Effects of treatment on stroke and coronary events. Solid squares represent treatment-to-control odds ratios in trials; the size of the squares is proportional to the number of events. RCTs—randomized controlled trials. (*Adapted from* Staessen *et al.* [4••]; with permission.)

mm Hg or greater compared with 119 for patients with smaller pulse pressure. Finally, the number of patients to treat for 5 years to prevent one major fatal and nonfatal cardiovascular event was similar in smokers and nonsmokers (30 vs 26) because of the opposite trends for stroke (85 vs 45) and coronary events (43 vs 72) [4••].

Conclusions

Drug treatment is justified in older patients whose systolic blood pressure is 160 mm Hg or higher. Absolute benefit is greater in men, in older patients, and in patients with previous cardiovascular complications or greater pulse pressure. In relative and absolute terms, treatment prevented stroke more effectively than it did coronary events. Furthermore, long-acting dihydropyridine calcium channel blockers constitute a valid alternative to diuretics and β-blockers in the primary prevention of cardiovascular complications in elderly hypertensive patients. In isolated systolic hypertension, calcium channel blockers may be particularly indicated in diabetic patients [19,31] and in those at risk of dementia [23,32] or renal dysfunction [25]. Recent trials showed that angiotensin converting enzyme inhibitors are equally effective as calcium channel blockers or the older drug classes (diuretics and β-blockers) in the overall prevention of the cardiovascular complications of hypertension [33•,34]. Whether this also applies to angiotensin II type 1 receptor antagonists is still unknown.

The positive correlation of systolic blood pressure with outcome, and the inverse correlation of diastolic blood pressure with mortality, suggest that in older hypertensive patients, pulse pressure is probably the major determinant of cardiovascular risk [4,15]. The implications of these findings for the management of hypertensive patients should be further investigated in randomized, controlled outcome trials in which the pulsatile component of blood pressure is differently affected by antihypertensive drug treatment, *eg*, nitrates [35] added to conventional antihypertensive agents.

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